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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,498	02/15/2000	HANS-PETER SCHWARZ	BHV-314.01	8060

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/424,498	SCHWARZ ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,32,35-37,39-41,43,44,64-66,68,69,72 and 74-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,32,39,40,43,44,64,65,68,69,72 and 74-78* is/are rejected.

7)☒ Claim(s) *35-37,41 and 66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Amendment filed April 1, 2005 has been entered. Claims 31-32, 35-37, 39-41, 43-44, 64-66, 68-69, 72, and 74-78 are pending and have been considered on the merits in this Office Action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 1, 2005 has been entered.

Declaration under 37 CFR 1.131

The Declaration of Peter Turecek under 37 C.F.R. 1.131 has been considered in this Office Action as discussed in the rejection below.

Rejections Withdrawn

The rejection of Claim 73 under 35 U.S.C. 112, second paragraph, because it depended from a rejected claim is withdrawn in light of its cancellation.

Rejections Maintained

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 31-32, 39-40, 43-44, 64-65, 72, and 74-76 are rejected under 35 U.S.C. 102(b) as being anticipated by Takagi et al. (Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-1020; ref. AY of IDS of Paper No. 6).

The rejection is maintained for reasons cited in the previous Office Actions and incorporated herein by reference. Applicants' arguments and the Declaration of Peter Turecek under 37 CFR 1.131 have been considered. Applicants argue that the examiner has provided litter reason or evidence to support the rejection. Applicants argue that the issue is not whether the Takagi et al. composition contains viruses but whether "it could be contaminated with viruses". Applicants argue that there is a difference in the risk of viral contamination associated with the claimed composition as compared to the Takagi et al. composition. These arguments and the Turecek Declaration have been considered but are not deemed persuasive because Applicants have not showed any patentable difference between the claimed composition and the Takagi et al. composition. The issue at hand is whether or not the claimed composition is patentably distinguishable from that of the Takagi et al. composition. Applicants argue that the Takagi et al. differs from that of the present invention because the Takagi et al. composition "could" contain viruses since it originated from a blood product. The

Turecek Declaration outlines that blood products carry a risk of contamination with viruses. However, the Turecek Declaration does not state or provide evidence that all blood products contain viruses and does not state or provide evidence that the Takagi et al. composition contains viruses. Evidence of record supports the assertion that the Takagi et al. composition does not contain viruses and is, therefore, patentably indistinguishable from the present claims. First, the blood products discussed in the Turecek Declaration and associated references differ from the Takagi et al. composition containing a purified protein in that the blood products are crude blood compositions (plasma or platelet compositions) subjected to very few processing steps whereas the Takagi et al. composition is a purified protein that has been subjected to multiple purification steps designed to remove contaminants. The Takagi et al. purification procedure has multiple steps. While the Turecek Declaration indicates that some viruses could pass through some steps and other viruses could pass through other steps, the Declaration does not state, provide evidence, or identify a single virus that could pass through all of the purification steps of Takagi et al. Second, contrary to Applicants assertion that no evidence has been provided to support the rejection, the examiner has noted previously that the SDS-PAGE gel in figure 1 (p. 6018 of Takagi et al. shows that pp-vWF is purified from other proteins. Most viruses contain proteins. Therefore, if the Takagi et al. composition were contaminated with viruses, these proteins would show up on the gel. Thus, the SDS-PAGE gel of Takagi et al. showing that the pp-vWF protein disclosed therein is purified from other proteins is considered

evidence that the composition does not contain viruses. Applicants have not provided evidence to the contrary.

The present claims are drawn to a product-by-process. As evidenced by the prior art, it appears that the vWF propolypeptide was very well known in the art at the time of the invention. While the vWF propolypeptide composition of the prior art appears to have been made by a process different than that claimed, the vWF propolypeptide known in the art is identical in structure and function to the presently claimed polypeptide and would inherently have the same properties and utilities as the polypeptide presently claimed. Applicants are reminded that something which is old does not become patentable upon the discovery of a new use. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) (see MPEP 2112). As explained in the previous rejection, the office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989). In the present case, there is no evidence

and no reason to believe that the Takagi et al. purified preparation of pp-vWF contains contaminated active viruses. .

In the present case, it appears that the claimed compositions are patentably indistinguishable from the prior art, absent evidence to the contrary. In the alternative, the claimed compositions would be obvious over the prior art as described below.

Claim Rejections - 35 USC § 103

Claims 31, 32, 39, 40, 43, 44, 64, 65, 72, and 74-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. (J. Biol. Chem. (1989) 264(11): 6017-6020) in view of EP 0 131 740 (cited in IDS of Paper No. 20), Blann et al. (Eur. J. Vasc. Surg. (1994) 8 : 10-15; cited in IDS) and Applicants admissions in the instant Specification.

The claims are rejected for reasons stated in the previous Office Actions.

As admitted in the Specification (p. 4, last paragraph), the purification of pp-vWF and virus removal or inactivation (p. 7, first paragraph) were very well known processes at the time of the invention. Therefore, the present issue at hand is whether or not one of ordinary skill in the art at the time of the invention would have been motivated to combine these well-known methods to make the claimed product.

Applicants argue that there is no motivation to combine the cited references because there is no evidence that would enable one to conclude that high vWF levels were a potential cause of arterial disease and because Blann et al. merely speculates that vWF has a role in atherosclerosis. Applicants contend that Blann et al. provides

evidence that vWF is a marker for and not a causal factor in atherosclerosis and that Blann et al. discloses that atherosclerosis has been reported in patients with von Willebrand disease.

These arguments have been considered but are not deemed persuasive for the following reasons:

Contrary to Applicants assertions, Blann et al. does provide suggestion that vWF is a causal factor in various types of atherosclerosis. First, Blann et al. emphasizes that vWF levels are raised in patients with atherosclerosis or related diseases (see paragraph bridging p. 12-13). Secondly, Blann et al. repeatedly suggests that high levels of vWF might predispose to or promote atherosclerosis (p. 13, 1st Col. Middle and last paragraph) and that reducing vWF levels might be a future therapeutic approach (p. 13, last paragraph). Applicants imply that Blann et al. concludes that there is no data in humans that would allow conclusion that low vWF levels protect from atherosclerosis. However, when the citation is read in its entirety and with the knowledge of the teachings of Takagi et al., this statement does not imply that Blann et al. concludes that vWF is not a causative factor. Blann et al. merely states that due to the complexity of von Willebrand disease (including that some patients do not have sufficiently severe disease to allow the hypothesis that low vWF would protect from atherosclerosis) and due to the added complexity of its treatment with vWF and factors that induce vWF release, von Willebrand disease cannot be used as a model for low vWF. Moreover, Takagi et al. teaches that pp-vWF is also low in patients with von Willebrand disease (p. 6017, Col. 2, first paragraph). Thus, one of ordinary skill in the art, with Blann et al. and

Takagi et al. in hand, would not conclude that vWF is not a causative factor in atherosclerosis and related diseases. Moreover, one of skill in the art would recognize that Blann et al. does suggest that reduction of vWF levels as a future therapeutic approach (p. 13, last paragraph).

Applicants argue that the present invention is based on the surprising discovery that pro-vWF does not counteract the effects of vWF but promotes vWF-associated coagulation and therefore, pro-vWf is useful for treating blood coagulation disorders.

This argument has been considered but is not deemed persuasive for the following reasons.

First, the Specification as originally filed does not indicate that the results indicating an increase of thrombin generation upon increases in pro-vWF in the plasma were surprising or unexpected. Mere conclusions in Applicants response that the results were unexpected are not entitled to the weight of conclusions accompanying the evidence, either in the Specification or in a declaration (MPEP 716.02(b) and Ex parte Gelles 22 USPQ2d 1318 (Bd. Pat. App. & Inter. 1992) cited therein). There is no evidence that the results described in the present Specification would have been surprising even with the knowledge of Takagi et al. The experiments described in the present application used different substrates (adding vWF and pro-vWF to vWF deficient plasma) and measured different effects (thrombin generation) from those of Takagi et al. (adding pro-vWF to platelet rich plasma from whole human blood anticoagulated with sodium citrate and measuring collagen induced platelet

aggregation). Moreover, Takagi et al. indicates that it was surprising to find that pro-vWF inhibited platelet aggregation (p. 6018, Col. 2, 2nd paragraph, lines 7-16).

Second, in response to applicant's argument that the inventors recognized a pharmacological function of the vWF propeptide not taught or suggested in the cited references, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Thrombus formation is a key event in the origin and progression of atherosclerosis (Blann et al. p. 10, first line). Mature vWF promotes collagen-platelet interaction and subsequently thrombus formation (see Takagi et al. p. 6018, Col. 2, 2nd paragraph) and is found at highest concentrations in severe atherosclerosis (Blann et al. (p. 12, Col. 1, 2nd paragraph). Takagi et al. found that pp-vWF effectively causes collagen to lose its platelet aggregation activity (Takagi et al. (Col. 2, beginning at line 10, 2nd paragraph). Thus, one of ordinary skill in the art would have had a reasonable expectation of success in using pp-vWF to counteract the platelet aggregation activities of vWF using pp-vWF since Takagi et al. provides evidence that pp-vWF has that activity. Blann et al. suggests that agents that lower vWF concentration might be useful in the treatment of atherosclerosis and related diseases and Takagi et al. teaches that pp-vWF counteracts mature vWF. Applicants contend that the examiner has not considered that Blann et al. suggest future studies rather than suggesting that new treatments would be successful. However, as explained in the previous Office Action,

all that is required is a motivation to make the composition claimed. The suggestion of Blann et al. and the knowledge of the teachings of Takagi et al., at the very least, would have motivated one of ordinary skill in the art to characterize the in vivo activities of pp-vWF as a potential therapeutic agent. Pursuing such research and trials, one of ordinary skill in the art would have wanted to obtain the most highly purified preparations of pp-vWF and would have included steps of eliminating any viral proteins that would contaminate the preparation and potentially cause erroneous results. In other words, in testing a potential therapeutic agent, one of ordinary skill in the art would have wanted to use a preparation that was representative of that that would be used in therapy. One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of obtaining highly pure preparations of pp-vWF since purification methods for pp-vWF were well known (as evidenced by Takagi et al.) and since virus removal methods were well known (as evidenced by EP 0 131 740). Therefore, in the present case, the combined references provide 1) methodology to make the claimed product (see Takagi et al. and EP 0 131 740), 2) a suggestion to use the claimed product as a pharmaceutical (see Takagi and Blann et al.), and 3) evidence suggesting such use would be successful (see Takagi et al. and Blann et al.).

The rejection is maintained.

Claim Rejections - 35 USC § 112

Claims 68, 69, 77 and 78 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. A pharmaceutical preparation for treating

blood coagulation disorders wherein the preparation comprises at least 10 nM or at least 100 nM pro-vWF is not enabled by the disclosure.

The rejection is maintained for the reasons cited in the Office Action mailed January 12, 2004.

As stated in the previous Office Action, the Specification does not provide guidance for a method of purification of pro-vWF and there is no evidence that such purification was routine in the art. Applicants argue that one of skill in the art could have used the teachings of Fischer et al. (FEBS Lett. 351: 345 (1994) and Megan (Thromb. Haemost. 59: 364 (1998) in the purification of pro-vWF. This argument has been considered but is not deemed persuasive because Fischer et al. and Megan et al. do not appear to teach a method of purifying pro-vWF. Fischer et al. teach a method of expressing full-length vWF in CHO cells and its subsequent isolation. Megan et al. teach a process for immunopurification of FVIII/vWF complex from plasma. These references do not teach that the processes taught therein could yield at least 10 nM pro-vWF. Thus, since Applicants state that the pro-vWF is highly labile (see Paper No. 19, p. 5) and there is no evidence of art prior to the invention that teaches the purification of pro-vWF, such a teaching would have been required in order for one of skill in the art to make the pro-vWF. The rejection is maintained.

Claim Objections

Claims 35-37 41 and 66 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

No Claims are allowable.

This is an RCE of applicant's earlier Application. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
June 6, 2005

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit. 1653